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Cardiovascular Manifestations of Hyperthyroidism Before and After Antithyroid Therapy

A Matched Case-Control Study

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Objectives This study sought to prospectively evaluate the prevalence of cardiovascular abnormalities in patients with overt hyperthyroidism before and after antithyroid therapy.

Background Overt hyperthyroidism is associated with recognized cardiovascular effects believed to be reversed by antithyroid therapy; however, increasing data suggest significant long-term cardiovascular mortality.

Methods A total of 393 (312 women, 81 men) consecutive unselected patients with overt hyperthyroidism were recruited and compared with 393 age- and gender-matched euthyroid control subjects. Hyperthyroid patients were re-evaluated after antithyroid therapy. Findings in patients and matched control subjects were compared at presentation, after treatment when patients had subclinical hyperthyroidism biochemically, and when patients were rendered biochemically euthyroid. All had a structured cardiovascular history and examination, including measurements of blood pressure (BP) and pulse rate. All had resting 12-lead electrocardiogram and 24-h digital Holter monitoring of cardiac rhythm.

Results A higher prevalence of cardiovascular symptoms and signs, as well as abnormal hemodynamic parameters, was noted among hyperthyroid patients at recruitment compared with control subjects. Cardiac dysrhythmias, especially supraventricular, were more prevalent among patients than among control subjects. Palpitation and dyspnea, postural decrease in systolic pressure, and atrial fibrillation (AF) remained more prevalent in treated hyperthyroid subjects with subclinical hyperthyroidism compared with control subjects, and remained more prevalent after restoration of euthyroidism. Predictors for successful reversion to sinus rhythm in those with AF associated with hyperthyroidism were lower BP measurements at recruitment and an initial hypothyroid state induced by antithyroid therapy. Mortality was higher in hyperthyroid subjects than in control subjects after a mean period of follow-up of 66.6 months.

Conclusions Cardiovascular abnormalities are common in patients with overt hyperthyroidism at presentation, but some persist despite effective antithyroid therapy. (J Am Coll Cardiol 2007;49:71–81) © 2007 by the American College of Cardiology Foundation

Hyperthyroidism is a common disorder with prominent cardiovascular effects including sinus tachycardia, systolic hypertension, changes in ventricular systolic and diastolic function, changes in peripheral vascular resistance, and predisposition to dysrhythmias, especially atrial fibrillation (AF) (1). In contrast with overt hyperthyroidism, the clinical impact of subclinical hyperthyroidism (low serum thyrotropin [TSH] with serum-free thyroxin [T_4]/serum-free tri-iodothyronine [T_3] within the reference range) has yet to be established, and treatment of subclinical hyperthyroidism remains controversial (2). The clinical significance of subclinical hyperthyroidism in those who have received treatment for overt hyperthyroidism is unknown.

Despite the perception that hyperthyroidism is reversible and without long-term consequences, increasing evidence suggests that it is associated with significant vascular morbidity and mortality after effective treatment (3–5), even in contemporary cohorts (6); persisting cardiovascular abnormalities may contribute to this vascular mortality. To date, no large prospective controlled study has defined the cardiovascular manifestations of hyperthyroidism before and after antithyroid therapy. The current study evaluated the prevalence of cardiovascular symptoms and signs, hemodynamic abnormalities, and dysrhythmias in overt hyperthy-

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Abbreviations and Acronyms

AF = atrial fibrillation
BP = blood pressure
ECG = electrocardiogram
IQR = interquartile range
LVH = left ventricular hypertrophy
nsVT = nonsustained ventricular tachycardia
PAF = paroxysmal atrial fibrillation
SVT = supraventricular tachycardia
T_4 = thyroxin
T_3 = tri-iodothyronine
TSH = thyrotropin

roidism before and after antithyroid therapy and compared findings with euthyroid control subjects. To examine the specific influence of hyperthyroidism in the absence of underlying vascular disease, we also analyzed findings excluding all subjects with known vascular disease (cardiovascular, cerebrovascular, or peripheral vascular). Mortality data were obtained on all subjects and compared between the hyperthyroid and control cohorts.

Methods

Subjects and study protocol. All patients referred to our Thyroid Clinic, University Hospital Birmingham, England, with a confirmed diagnosis of overt hyperthyroidism were eligible, enabling us to recruit a large unselected cohort. Overt hyperthyroidism was defined as increased serum-free T_4 and/or T_3 concentration in the presence of an undetectable TSH level. Patients with overt hyperthyroidism of any etiology were investigated and were categorized by simple clinical and immunologic criteria into 3 diagnostic groups (7): Graves disease (biochemical hyperthyroidism with 2 of the following: palpable diffuse goiter, significant titer of thyroid peroxidase/thyroglobulin autoantibodies, presence of dysthyroid eye disease), toxic nodular hyperthyroidism (hyperthyroidism with palpable nodular goiter), and hyperthyroidism of indeterminate etiology (neither criteria fulfilled). Hyperthyroid subjects were treated with antithyroid drugs/radioiodine (8). An age- and gender-matched euthyroid control group, free of past or current thyroid dysfunction, was recruited from staff members working at the hospital or medical school or their relatives and from a local community center; the latter represented a wide spectrum of the elderly community, both affluent and disadvantaged, attending for social reasons. The control group had the same investigations as the hyperthyroid cohort. Approval for the study was obtained from the local research ethics committee, and all subjects provided informed consent.

All had a structured cardiovascular history and examination, resting 12-lead electrocardiogram (ECG) (Pagewriter 200, Hewlett-Packard, Palo Alto, California), digital ambulatory 24-h Holter monitoring (Life Card CF, Reynolds Medical, Hertford, England), and assessment of thyroid function using the Bayer ACS 180/Advia Centaur System (Newbury, England). Normal ranges for serum-free T_4, T_3, and TSH were 9 to 20 pmol/l, 3.5 to 6.5 pmol/l, and 0.5 to 5.0 mU/l, respectively.

Hyperthyroid patients (but not control subjects) were re-evaluated after antithyroid therapy with repeat assessment at approximately 6 and 9 months after recruitment. Patients found to show the biochemistry of subclinical hyperthyroidism (suppressed TSH with normal free T_4/T_3) during antithyroid therapy were compared with matched control subjects. Similarly, those rendered biochemically euthyroid at follow-up were compared with matched control subjects. Those patients found to have AF at presentation were followed up to evaluate the course of their dysrhythmia. A further analysis was performed confined to subjects without known vascular disease.

All subjects were registered with the UK Office for National Statistics as described before (3,6) to obtain mortality data during follow-up. The underlying cause of death was coded according to the International Classification of Diseases (9).

Cardiovascular history and examination. Information was collected using a structured questionnaire derived from previous studies (10,11). Cardiovascular symptoms had to be of new onset coincident with the onset of hyperthyroidism. Specific symptoms evaluated included dyspnea, chest pain, palpitation, orthopnea, paroxysmal nocturnal dyspnea, cough, and pedal edema. History of vascular disease (treated hypertension, ischemic heart disease, cerebrovascular disease, congestive cardiac failure) and diabetes mellitus were recorded, as was a family history of vascular disease in first- or second-degree relatives <70 years old. Smoking history was documented as never, previous, or current smoker. Findings noted on examination included presence of raised venous pressure (>2 cm above sternal notch at 45°), displaced apex beat (beyond 5th intercostal space, midclavicular line), cardiac murmurs, and abnormal chest auscultation (crepitations or wheeze). Resting pulse rate, and lying and standing (after 5 min) blood pressure (BP) measurements were taken, the latter with an automatic monitor (Dinamap Pro200, GE Systems, Miami, Florida). The systolic pressure difference was calculated as standing-lying systolic pressure, diastolic pressure difference as lying-standing diastolic pressure, and pulse rate change as standing-lying heart rate. All subjects were evaluated by a single investigator (F.O.).

Cardiac rhythm assessment. The ECG abnormalities were coded using the Minnesota classification (12); presence of pathological Q waves, abnormal cardiac axis, left or right bundle branch block, left ventricular hypertrophy (LVH), and heart block were noted. All Holter data were analyzed using the Pathfinder 700 Analyzer (Reynolds Medical) and manually edited to correct inaccuracies. Presence of >240 premature atrial or ventricular ectopic beats/24-h period was classified as significant (13). Atrial salvoes were defined as more than 3 consecutive premature atrial beats (14) and supraventricular tachycardia (SVT) as ≥10 consecutive supraventricular premature beats (15). Nonsustained ventricular tachycardia (nsVT) was defined as more than 8 consecutive ventricular ectopic beats lasting <30 s and ventricular salvoes as 4 to 8 consecutive ectopic beats, allowing detection of short and long bursts of ventricular

ectopic activity. Sustained ventricular tachycardia was defined as consecutive ventricular beats lasting ≥30 s (16). The number of isolated ventricular and atrial premature beats was evaluated, along with the presence of second- or third-degree heart block.

Statistical analysis. All data were analyzed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, Illinois); tests of normality were performed using Minitab version 13.0 (Minitab Inc., State College, Pennsylvania). Continuous variables assuming a normal distribution (pulse rate, BP) were expressed as mean ± SEM; those with a non-normal distribution (age, serum-free T_4/T_3) were expressed as median ± interquartile range (IQR). Nominal data were presented as number and percentage of total. Comparisons between nonparametric matched data were made using the Wilcoxon signed rank (continuous data) and McNemar tests (nominal data). Comparisons between normally distributed matched data were made using the paired *t* test. Multivariate conditional logistic regression analysis (forward selection) was used to identify independent risk predictors for cardiovascular symptoms and rhythm abnormalities. Bonferroni corrections were made to significance levels where multiple comparisons were used (17); the latter included all comparisons of cardiovascular symptoms, hemodynamic parameters, and rhythm analysis.

Results

Baseline characteristics. A total of 396 unselected consecutive patients with overt hyperthyroidism were eligible, of whom 393 were recruited (April 1999 to April 2002); 3 declined to participate. Those recruited were age-matched (within 2 years) and gender-matched to euthyroid control subjects (312 women, 81 men); 180 were recruited from staff members or their relatives, 213 from the community center. Median age of the hyperthyroid and control cohorts was similar (49.0 years: IQR 36 to 63 years vs. 49.0 years: IQR 35 to 63 years, $p > 0.9$); age range 17 to 89 years for both groups. A total of 233 hyperthyroid patients received radioiodine, and 378 received carbimazole/propylthiouracil. Of the 393 patients recruited, 147 had Graves disease, 88 had toxic nodular goiter, and 158 had hyperthyroidism of indeterminate origin. Median serum-free T_4 and T_3 at diagnosis in the hyperthyroid cohort were 37.5 pmol/l (IQR 27 to 52 pmol/l) and 11.4 pmol/l (IQR 8 to 18 pmol/l), respectively; serum TSH was undetectable in all. Serum-free T_4 and TSH were within the normal range for all control subjects (median 13.8 pmol/l, IQR 13 to 15 pmol/l vs. 1.6 mU/l, IQR 1 to 2 mU/l, respectively). The prevalence of vascular diseases was similar between the 2 cohorts; there were more current smokers in the hyperthyroid cohort and fewer never smokers than control subjects. After excluding all patients with known vascular disease, there were 320 hyperthyroid subjects; of these, 266 had matched control subjects without vascular disease available for comparison (Table 1).

A total of 110 showed the biochemistry of subclinical hyperthyroidism when evaluated during follow-up (27.1 ± 2.1 weeks after first evaluation; 92 women, 18 men). The median serum-free T_4 and T_3 were 16.4 pmol/l, IQR 15 to 19 pmol/l and 5.5 pmol/l, IQR 5 to 6 pmol/l, and TSH was undetectable in all. A total of patients were rendered biochemically euthyroid at the time of re-evaluation (36.9 ± 1.6 weeks after recruitment; 163 women, 44 men). The median serum-free T_4 and T_3 were 12.8 pmol/l, IQR 11 to 15 pmol/l and 4.1 pmol/l, IQR 3 to 5 pmol/l; all had normal TSH (median 1.8 mU/l, IQR 0.8 to 3.1 mU/l). Comparisons of these patients were made with their respective control subjects. Baseline characteristics of those patients lost to follow-up (n = 69) or not re-evaluated when subclinically hyperthyroid or euthyroid after treatment were not different compared with those undergoing repeat eval-

Table 1 Comparison of Baseline Characteristics Between the Hyperthyroid and Control Cohorts*

	Total Cohort			Cohort Without Vascular Disease		
	Thyroid n = 393	Control n = 393	p Value	Thyroid† n = 266	Control n = 266	p Value
Age at recruitment (yrs)	49.0 (36–63)	49.0 (35–63)	0.9	42.0 (32–52)	42.0 (33–53)	0.9
Male	81	81		53	53	
Female	312	312		213	213	
Undetectable thyrotropin	393	0		266	0	
Serum-free T_4 (pmol/l)	37.5 (27–52)	13.8 (13–15)		36.2 (25–49)	14.0 (13–15)	
Serum-free T_3 (pmol/l)	11.4 (8–18)	Not measured		11.1 (8–17)	Not measured	
Known vascular disease	73 (19%)	71 (18%)	0.9	0	0	
Diabetes mellitus	23 (6%)	11 (3%)	0.1	9 (3%)	2 (1%)	0.1
Family history of vascular disease	269 (68%)	278 (71%)	0.7	181 (68%)	189 (71%)	0.6
Smoking history						
Current smoker	115 (29%)	58 (15%)	<0.0001	89 (33%)	39 (15%)	<0.0001
Never smoked	148 (38%)	218 (55%)	<0.0001	102 (38%)	157 (59%)	<0.0001
Past smoker	130 (33%)	117 (30%)	0.3	75 (28%)	70 (26%)	0.7

*Values expressed as median with interquartile-range or n (%). †Excludes those without a matched euthyroid control.
T_3 = tri-iodothyronine; T_4 = thyroxin.

uation in terms of age, gender, known vascular disease, and diabetes (data not shown).

Cardiovascular symptoms and signs. Cardiovascular symptoms and signs (Table 2) were more prevalent in hyperthyroid patients when first evaluated compared with matched control subjects, especially palpitation, which was the most prevalent. Comparison of findings from treated patients with subclinical hyperthyroidism and their control subjects showed persistent palpitation, dyspnea, and cough. Palpitation and dyspnea persisted even at assessment after restoration of biochemical euthyroidism. After excluding all subjects with known vascular disease, cardiovascular symptoms remained more prevalent among hyperthyroid patients at recruitment compared with control subjects. Symptoms, notably palpitation and dyspnea, were also more prevalent compared with control subjects in subjects evaluated when subclinically hyperthyroid and when rendered euthyroid.

Multivariate logistic regression analysis identified independent predictors of cardiovascular symptoms both at recruitment and after restoration of euthyroidism. Age >50 years ($p < 0.0001$), female gender ($p = 0.002$), and serum-free T_4 >30 pmol/l ($p = 0.01$) all predicted palpitation at recruitment. Dyspnea at recruitment was predicted by past history of angina ($p = 0.001$) and congestive cardiac failure ($p < 0.0001$), as well as lying diastolic BP >90 mm Hg at recruitment ($p = 0.01$). Past history of congestive cardiac failure and ischemic heart disease (both $p < 0.01$) predicted persisting chest pain and dyspnea after restoration of euthyroidism. Past history of vascular disease ($p < 0.0001$), female gender ($p < 0.01$), and age >50 years ($p < 0.001$) also predicted cardiac symptoms among euthyroid control subjects. After excluding those with known vascular disease, age >50 years ($p < 0.005$) and female gender ($p < 0.01$) independently predicted palpitation at recruitment among hyperthyroid patients; female gender ($p = 0.001$) and serum T_4 >30 pmol/l ($p = 0.005$) were predictive of dyspnea at recruitment, and current smoking ($p < 0.05$) predicted persisting dyspnea after restoration of euthyroidism. The etiology of hyperthyroidism was not predictive of the presence of cardiac symptoms either at presentation or after antithyroid therapy (data not shown).

Hemodynamic findings. Resting pulse rate and lying systolic BP were higher in hyperthyroid patients at recruitment compared with matched control subjects (82 ± 1 beats/min vs. 73 ± 1 beats/min, $p < 0.0001$, and 137 ± 1 mm Hg vs. 129 ± 1 mm Hg, $p < 0.0001$) (Table 3). A postural decrease in systolic pressure was noted in hyperthyroid patients compared with control subjects (−4 ± 1 mm Hg vs. 2 ± 1 mm Hg, $p < 0.0001$). Resting pulse rate and lying systolic BP remained higher among patients with subclinical

Table 2 Comparison of Cardiovascular Symptoms Between Hyperthyroid and Control Cohorts

	Total Cohort			Cohort Without Vascular Disease		
Findings	Thyroid Cohort n (%)	Control Cohort n (%)	p Value	Thyroid Cohort n (%)	Control Cohort n (%)	p Value
Recruitment	393	393		266	266	
Palpitation	288 (73)	79 (20)	<0.0001	199 (75)	52 (20)	<0.0001
Chest pain	97 (25)	42 (11)	<0.0001	63 (24)	28 (11)	<0.0001
Dyspnea	236 (60)	53 (14)	<0.0001	154 (58)	33 (12)	<0.0001
Cough	137 (35)	45 (12)	<0.0001	83 (31)	32 (12)	<0.0001
Orthopnea	24 (6)	4 (1)	<0.0001	9 (3)	2 (1)	0.07
Displaced apex	14 (4)	4 (1)	<0.01	6 (2)	0	<0.05
Cardiac murmur	59 (15)	21 (5)	<0.0001	32 (12)	15 (6)	<0.01
Chest wheeze/crepitus	36 (9)	6 (2)	<0.0001	18 (7)	2 (1)	<0.0001
SCH follow-up	110	110		72	72	
Palpitation	49 (45)	20 (18)	<0.0001	33 (46)	14 (19)	<0.002
Chest pain	15 (14)	12 (11)	0.4	9 (13)	6 (8)	0.6
Dyspnea	26 (24)	16 (15)	<0.002	19 (26)	13 (18)	0.3
Cough	22 (20)	12 (11)	<0.05	14 (19)	6 (8)	0.1
Orthopnea	4 (4)	1 (1)	0.1	3 (4)	1 (1)	0.6
Displaced apex	1 (1)	1 (1)	0.9	1 (1)	0	0.9
Cardiac murmur	9 (8)	6 (5)	0.1	5 (7)	2 (3)	0.5
Chest wheeze/crepitus	2 (2)	2 (2)	0.9	1 (1)	0	0.9
Euthyroid follow-up	207	207		133	133	
Palpitation	64 (31)	43 (21)	<0.0007	45 (34)	27 (20)	<0.03
Chest pain	32 (16)	22 (11)	0.2	17 (13)	17 (13)	0.9
Dyspnea	61 (30)	27 (13)	<0.0001	37 (28)	17 (13)	<0.005
Orthopnea	7 (3)	4 (2)	0.5	3 (2)	2 (2)	0.9
Displaced apex beat	1 (0.5)	3 (1)	0.6	0	0	0.9
Cardiac murmur	16 (8)	13 (6)	0.7	7 (5)	8 (6)	0.9
Chest wheeze/crepitus	9 (4)	5 (2)	0.4	3 (2)	2 (2)	0.9

SCH = subclinical hyperthyroidism.

Table 3 Comparison of Hemodynamic Parameters Between Hyperthyroid and Control Cohorts

Parameter	Total Cohort			Cohort Without Vascular Disease		
	Thyroid Mean ± SEM	Control Mean ± SEM	p Value	Thyroid Mean ± SEM	Control Mean ± SEM	p Value
Recruitment	393	393		266	266	
Resting pulse rate	82 ± 1	73 ± 1	<0.0001	81 ± 1	73 ± 1	<0.0001
Lying systolic pressure	137 ± 1	129 ± 1	<0.0001	131 ± 1	127 ± 1	<0.009
Lying diastolic pressure	76 ± 1	75 ± 1	0.7	74 ± 1	74 ± 1	0.7
Pulse rate change	6 ± 4	4 ± 1	0.5	6 ± 4	3 ± 2	0.5
Systolic pressure difference	−4 ± 1	2 ± 1	<0.0001	−2 ± 1	2 ± 1	<0.0001
Diastolic pressure difference	4 ± 1	4 ± 1	0.9	5 ± 1	4 ± 1	0.4
SCH follow-up	110	110		72	72	
Resting pulse rate	76 ± 1	73 ± 1	<0.01	76 ± 1	72 ± 1	<0.05
Lying systolic pressure	137 ± 2	130 ± 1	<0.01	132 ± 3	126 ± 2	<0.05
Lying diastolic pressure	76 ± 1	75 ± 1	0.8	75 ± 2	74 ± 1	0.6
Pulse rate change	9 ± 2	7 ± 1	0.4	5 ±	1 ± 1	0.1
Systolic pressure difference	−3 ± 1	1 ± 1	<0.005	−2 ± 1	1 ± 1	0.08
Diastolic pressure difference	3 ± 1	4 ± 1	0.5	3 ± 1	3 ± 1	0.9
Euthyroid follow-up	207	207		133	133	
Resting pulse rate	73 ± 1	73 ± 1	0.9	72 ± 2	73 ± 1	0.7
Lying systolic pressure	134 ± 2	131 ± 1	0.1	128 ± 2	128 ± 2	0.9
Lying diastolic pressure	74 ± 1	75 ± 1	0.4	73 ± 1	73 ± 1	0.9
Pulse rate change	11 ± 4	5 ± 2	0.2	11 ± 4	5 ± 2	0.6
Systolic pressure difference	−2 ± 1	3 ± 1	<0.005	1 ± 1	2 ± 1	0.4
Diastolic pressure difference	5 ± 1	4 ± 1	0.6	5 ± 1	5 ± 1	0.8

Pulse rates measured in beats/min, blood pressures in mm Hg.
SCH = subclinical hyperthyroidism.

hyperthyroidism during follow-up than control subjects (76 ± 1 beats/min vs. 73 ± 1 beats/min, $p < 0.01$, and 137 ± 2 mm Hg vs. 130 ± 1 mm Hg, $p < 0.01$); the postural decrease in systolic pressure also persisted (−3 ± 1 mm Hg vs. 1 ± 1 mm Hg, $p < 0.005$). No differences in hemodynamic parameters remained at the euthyroid assessment except the postural decrease in systolic pressure (−2 ± 1 mm Hg vs. 3 ± 1 mm Hg, $p < 0.0001$). Excluding those with vascular disease, findings for BP and resting pulse rate remained unchanged at recruitment and subclinical/euthyroid follow-up; the postural decrease in systolic pressure among patients persisted but was no longer significant at follow-up.

Cardiac rhythm analysis. One hyperthyroid subject had a permanent pacemaker and was excluded from analysis. Hyperthyroid subjects at presentation showed a higher prevalence of AF on ECG compared with control subjects (Table 4). Of the 392 patients investigated by Holter monitor, 333 (85%) had analyzable data; 311 of these were used in matched comparison with control subjects. The minimum, mean, and maximum 24-h heart rates were higher among patients. The prevalence of AF and atrial salvoes was higher in patients than in control subjects, but other dysrhythmias were similar. After excluding those with known vascular disease, AF and atrial salvoes were still more prevalent among hyperthyroid patients than among control subjects.

Of the 110 patients with subclinical hyperthyroidism during follow-up, 1 had a permanent pacemaker and was excluded from analysis. Patients had a higher prevalence of AF on ECG compared with control subjects. A total of 88 patients (81%) had analyzable Holter data; 85 were matched with control subjects. The prevalence of AF on Holter and minimum heart rate remained higher compared with control subjects; differences were no longer apparent after excluding those with vascular disease (Table 5).

One of the 207 patients rendered biochemically euthyroid at follow-up had a permanent pacemaker and was excluded from analysis. Comparison of the remaining 206 matched patient-control data showed a higher prevalence of AF on ECG in euthyroid patients than in control subjects. A total of 146 (71%) patients had analyzable Holter data; 133 were matched with control subjects. Comparison of Holter data showed no differences between the 2 groups; however, not all patients found to have AF on ECG had Holter data available at this comparison. Excluding those with vascular disease showed no differences in prevalence of ECG or Holter data between patients and control subjects (Table 6).

Independent predictors of dysrhythmias at recruitment included age >50 years (atrial salvoes, significant atrial or ventricular ectopic beats, $p < 0.0001$), known vascular disease (ventricular salvoes, $p < 0.05$), diastolic BP >90 mm Hg at recruitment (nsVT, $p < 0.03$), and increased venous pressure (SVT, $p < 0.002$). Independent predictors of persisting dysrhythmias at euthyroidism included age >50 years (atrial salvoes, $p < 0.005$), serum-free T_4 >40 pmol/l at presentation (nsVT, $p < 0.05$), and diabetes (SVT, $p < 0.01$). Etiology of hyperthyroidism was not

Table 4 Comparison of Electrocardiogram and Holter Data of Hyperthyroid Patients With Matched Controls

	Total Cohort			Cohort Without Vascular Disease		
Electrocardiogram Findings	Thyroid n = 392	Control n = 392	p Value	Thyroid n = 265	Control n = 265	p Value
AF	24 (6%)	3 (0.8%)	<0.0001	6 (2%)	1 (0.4%)	0.1
Abnormal cardiac axis	21 (5%)	17 (4%)	0.6	6 (2%)	9 (3%)	0.6
Left ventricular hypertrophy	7 (2%)	1 (0.3%)	0.1	2 (1%)	0	0.5
Right bundle branch block	7 (2%)	8 (2%)	0.9	3 (1%)	5 (2%)	0.7
Left bundle branch block	2 (0.5%)	4 (1%)	0.6	0	1 (0.4%)	0.9
Pathological Q-wave	7 (2%)	1 (0.3%)	0.1	0	0	0.9
24-h Holter findings	311	311		206	206	
Minimum heart rate (beats/min)	60 ± 1	54 ± 1	<0.0001	59 ± 1	53 ± 1	<0.0001
Mean heart rate (beats/min)	81 ± 2	73 ± 1	<0.0001	82 ± 2	76 ± 2	<0.03
Maximum heart rate (beats/min)	128 ± 1	122 ± 1	<0.0001	129 ± 2	124 ± 1	<0.02
Total AF	22 (7%)	4 (1%)	<0.001	6 (3%)	2 (1%)	0.3
Persistent AF	16 (5%)	3 (1%)	<0.009	5 (2.5%)	1 (0.5%)	0.2
Paroxysmal AF	6 (2%)	1 (0.3%)	0.1	1 (0.5%)	1 (0.5%)	0.9
Single ventricular ectopics	316 ± 92	128 ± 31	0.06	109 ± 48	114 ± 35	0.9
Single atrial ectopics*	47 ± 9	66 ± 16	0.3	31 ± 10	52 ± 18	0.3
>240 ventricular ectopics	29 (9%)	26 (8%)	0.8	11 (5%)	15 (7%)	0.6
>240 atrial ectopics*	16 (5%)	14 (5%)	0.9	7 (4%)	8 (4%)	0.9
Ventricular salvoes	8 (3%)	2 (1%)	0.1	3 (1%)	2 (1%)	0.9
Atrial salvoes*	69 (23%)	40 (14%)	<0.001	37 (18%)	20 (10%)	<0.03
Supraventricular tachycardia*	3 (1%)	3 (1%)	0.9	3 (1%)	0	0.3
Nonsustained ventricular tachycardia	5 (2%)	0	0.1	3 (1%)	0	0.3
Second- or third-degree block	1 (0.2%)	0	0.2	0	0	0.9

All values expressed as n (%) or mean ± SEM. *Excluding persistent atrial fibrillation (AF) on Holter monitoring.

predictive of the presence of dysrhythmias either at presentation or after antithyroid therapy (data not shown).

Use of drugs affecting cardiac rate or rhythm. No subjects were prescribed class I antiarrhythmic therapy or amiodarone, and no differences were noted in use of class IV drugs (verapamil, diltiazem) at recruitment or subsequent follow-up. Use of beta-blockers was more frequent in hyperthyroid patients at recruitment and subclinical hyperthyroidism compared with control subjects (25% vs. 6%, $p < 0.0001$ and 19% vs. 5%, $p < 0.0001$, respectively). Use of sotalol when patients were rendered euthyroid was higher than in control subjects (3% vs. 0.5%, $p < 0.01$). Digoxin use was higher among patients at recruitment and at subclinical hyperthyroid and euthyroid follow-up compared with control subjects (4% vs. 0.2%, $p < 0.0001$; 4% vs. 1%, $p < 0.005$; 4% vs. 0.5%, $p < 0.0001$, respectively). Further comparisons excluding all subjects prescribed these drugs did not affect any of the overall cardiovascular findings at recruitment, during subclinical hyperthyroidism, or during euthyroid follow-up (table available on request).

AF and hyperthyroidism. Twenty-nine patients (7.3%) were found to have AF at recruitment, of whom 21 had newly diagnosed AF (15 persistent AF, 6 paroxysmal atrial fibrillation [PAF]), and 8 previously known persistent or permanent AF (all euthyroid at original diagnosis). Patients with AF were older than those without (69.0 years, IQR 65 to 76 years vs. 49.5 years, IQR 36 to 63 years, $p < 0.0001$) and had a higher prevalence of known vascular disease (51% vs. 21%, $p < 0.0001$), especially congestive cardiac failure (23% vs. 2%, $p < 0.0001$). Measurements of BP at presentation were higher among those with AF than without (147 ± 5 mm Hg vs. 136 ± 1 mm Hg, $p < 0.02$ and 83 ± 3 mm Hg vs. 75 ± 1 mm Hg, $p < 0.005$); those with AF showed a greater prevalence of LVH on ECG (11% vs. 1%, $p < 0.001$). Factors independently predicting AF at presentation of hyperthyroidism were increasing age ($p < 0.0001$), history of cardiac failure ($p < 0.0001$), diabetes ($p < 0.02$), elevated systolic or diastolic BP ($p < 0.005$), and LVH on ECG ($p < 0.02$).

The outcome of subjects with AF in terms of rhythm is shown in Figure 1. Seven of the 8 with previously known AF remained in AF. Of the 15 patients with newly diagnosed persistent AF, 10 remained in AF (6 rendered euthyroid, 4 with suppressed TSH) and 5 reverted to sinus rhythm (all rendered euthyroid). Of the 6 with PAF, only 1 had PAF at follow-up (all rendered euthyroid). Four patients underwent electrical cardioversion once euthyroid: 2 maintained sinus rhythm at follow-up, and 2 achieved sinus rhythm only transiently (1 prescribed verapamil, 1 no drug therapy). Electrical cardioversion was declined by 5 (because of age or general frailty, median age 75 years, IQR 73 to 79 years) and not offered to 5 on clinical grounds (dilated atria on ECG and/or known permanent AF). The majority of AF patients were commenced on warfarin (n = 24, 83%); 5 received aspirin because of contraindications or refusal to take warfarin.

Overall, of the 29 patients with AF, 11 successfully achieved and maintained sinus rhythm (no further AF on

Table 5 Comparison of Electrocardiogram and Holter Data Between Patients With Biochemical Subclinical Hyperthyroidism During Follow-Up With Matched Controls

	Total Cohort			Cohort Without Vascular Disease		
Electrocardiogram Findings	Thyroid n = 109	Control n = 109	p Value	Thyroid n = 71	Control n = 71	p Value
AF	8 (7%)	1 (1%)	<0.0001	3 (4%)	0	0.3
Abnormal cardiac axis	5 (5%)	5 (5%)	0.9	2 (3%)	3 (4%)	0.9
Left ventricular hypertrophy	0	0	0.9	0	0	0.9
Right bundle branch block	2 (2%)	2 (2%)	0.9	1 (1%)	1 (1%)	0.9
Left bundle branch block	1 (1%)	2 (2%)	0.9	0	0	0.9
Pathological Q-wave	0	0	0.9	0	0	0.9
24-h Holter findings	85	85		57	57	
Minimum heart rate (beats/min)	57 ± 1	54 ± 1	<0.002	58 ± 2	56 ± 1	0.2
Mean heart rate (beats/min)	78 ± 2	76 ± 2	0.7	81 ± 3	79 ± 2	0.5
Maximum heart rate (beats/min)	122 ± 3	122 ± 1	0.9	127 ± 4	124 ± 2	0.5
Total AF	5 (6%)	1 (1%)	<0.001	3 (5%)	0	0.3
Persistent AF	4 (5%)	1 (1%)	<0.01	3 (5%)	0	0.3
Paroxysmal AF	1 (1%)	0	0.1	0	0	0.9
Single ventricular ectopics	87 ± 26	170 ± 48	0.2	45 ± 21	27 ± 9	0.4
Single atrial ectopics*	28 ± 8	101 ± 36	0.2	14 ± 7	48 ± 25	0.2
>240 ventricular ectopics	8 (9%)	9 (11%)	0.8	3 (5%)	2 (4%)	0.9
>240 atrial ectopics*	3 (4%)	5 (6%)	0.6	1 (2%)	3 (5%)	0.6
Ventricular salvoes	0	0	0.9	0	0	0.9
Atrial salvoes*	14 (17%)	13 (16%)	0.9	5 (9%)	4 (7%)	0.9
Supraventricular tachycardia*	3 (4%)	2 (2%)	0.4	2 (4%)	0	0.5
Nonsustained ventricular tachycardia	4 (5%)	0	0.1	2 (4%)	0	0.5
Second- or third-degree block	0	0	0.9	0	0	0.9

All values expressed as n (%) or mean ± SEM. *Excluding persistent atrial fibrillation (AF) on Holter monitoring.

Holter monitoring) at follow-up: 5 spontaneously (18.0 ± 2.9 weeks after recruitment), 4 on rate/rhythm drug therapy (19.8 ± 6.1 weeks after recruitment; 3 sotalol, 1 verapamil), and 2 electrically cardioverted (neither on concomitant antiarrhythmic therapy). These patients were younger than those remaining in AF (68.0 years, IQR 63 to 74 years vs. 75.0 years, IQR 72 to 79 years, $p < 0.006$) and more likely to have been rendered initially hypothyroid by antithyroid drug therapy (defined as serum TSH >5.5 mU/l and low free T_4) compared with those remaining in AF (58% vs. 13%, $p < 0.02$). Independent predictors of successful reversion to sinus rhythm were lower systolic BP ($p < 0.02$) and an initial hypothyroid state induced by antithyroid therapy ($p < 0.009$). Age, gender, biochemical severity of hyperthyroidism, smoking history, known vascular disease, and diabetes were not predictive. Seven patients with AF died during follow-up of congestive cardiac failure (n = 1), cerebrovascular accident (n = 1), ischemic heart disease (n = 1), malignant neoplasm (n = 2), and septicemia (n = 2).

Mortality data at follow-up. After a mean follow up of 66.6 ± 0.6 months, 26 patients died compared with 12 control subjects ($p < 0.01$). The causes of death among patients were malignancy (n = 7), ischemic heart disease (n = 5), cerebrovascular disease (n = 1), aortic stenosis (n = 1), sepsis (n = 10), carbon monoxide poisoning (n = 1), and gastrointestinal bleed (n = 1). Causes of death among control subjects were malignancy (n = 7), ischemic heart disease (n = 2), acute aortic dissection (n = 1), sepsis (n = 1), and aortic stenosis (n = 1).

After excluding all subjects with known vascular disease, 10 patients died during follow-up compared with 3 control subjects ($p = 0.09$). The causes of death among patients were sepsis (n = 4), ischemic heart disease (n = 1), aortic stenosis (n = 1), malignancy (n = 3), and carbon monoxide poisoning (n = 1); causes of death among euthyroid control subjects were malignancy (n = 1), sepsis (n = 1), and acute aortic dissection (n = 1).

Discussion

Overt hyperthyroidism is associated with cardiovascular symptoms and changes in cardiovascular hemodynamics (1), which were confirmed by the present study. However, data on the effect of antithyroid therapy on these findings are sparse and generally reflect small studies (18–20). We showed that despite restoration of biochemical euthyroidism, previously hyperthyroid patients continue to experience significant cardiovascular symptoms, in particular palpitation, dyspnea, and cough. Symptoms persist even in those without a preceding history of vascular disease. A recent study found a high prevalence of pulmonary hypertension in hyperthyroidism, which was corrected after treatment (21). The dyspnea reported in overt hyperthyroidism in part may be the result of elevated pulmonary pressure. Low efficiency of cardiopulmonary function, respiratory muscle weakness,

Table 6 Comparison of Electrocardiogram and Holter Data Between Patients Rendered Euthyroid at Follow-Up With Matched Controls

	Total Cohort			Cohort Without Vascular Disease		
Electrocardiogram Findings	Thyroid n = 206	Control n = 206	p Value	Thyroid n = 133	Control n = 133	p Value
AF	10 (5%)	2 (1%)	<0.05	1 (1%)	0	0.9
Abnormal cardiac axis	8 (4%)	9 (5%)	0.9	5 (4%)	5 (4%)	0.9
Left ventricular hypertrophy	3 (2%)	0	0.3	2 (2%)	0	0.5
Right bundle branch block	2 (1%)	6 (3%)	0.3	0	4 (3%)	0.2
Left bundle branch block	1 (0.5%)	1 (0.5%)	0.9	0	1 (1%)	0.9
Pathological Q-wave	1 (0.5%)	0	0.9	0	0	0.9
24-h Holter findings	133	133		85	85	
Minimum heart rate (beats/min)	54 ± 1	54 ± 1	0.9	55 ± 1	54 ± 1	0.4
Mean heart rate (beats/min)	76 ± 2	72 ± 2	0.1	79 ± 3	76 ± 3	0.3
Maximum heart rate (beats/min)	120 ± 1	122 ± 2	0.4	123 ± 2	125 ± 2	0.5
Total AF	4 (3%)	1 (1%)	0.8	1 (1%)	0	0.9
Persistent AF	3 (2%)	1 (1%)	0.6	1 (1%)	0	0.9
Paroxysmal AF	1 (1%)	0	0.9	0	0	0.9
Single ventricular ectopics	103 ± 57	171 ± 55	0.4	26 ± 10	126 ± 51	0.06
Single atrial ectopics*	25 ± 6	62 ± 25	0.1	13 ± 5	61 ± 34	0.2
>240 ventricular ectopics	7 (5%)	15 (11%)	0.1	5 (6%)	9 (11%)	0.1
>240 atrial ectopics*	5 (4%)	5 (4%)	0.9	1 (1%)	3 (4%)	0.6
Ventricular salvoes	0	1 (1%)	0.9	0	1 (1%)	0.9
Atrial salvoes*	24 (18%)	19 (15%)	0.7	11 (13%)	11 (13%)	0.9
Supraventricular tachycardia*	4 (3%)	2 (2%)	0.6	2 (3%)	0	0.5
Nonsustained ventricular tachycardia	0	0	0.9	0	0	0.9
Second or third-degree block	1 (1%)	0	0.9	0	0	0.9

All values expressed as n (%) and mean ± SEM. *Excluding persistent atrial fibrillation (AF) on Holter monitoring.

and impaired exercise capacity have also been shown in hyperthyroidism and may also explain this symptom (20); these changes were found to be reversible with treatment in the latter study.

In the present study, hyperthyroid patients showed a significant postural decrease in systolic BP suggesting an abnormality of peripheral vascular resistance, this finding being absent in the cohort of hyperthyroid subjects without known vascular disease after antithyroid therapy. A marked decrease in peripheral vascular resistance has been reported in overt hyperthyroidism, but the mechanism remains uncertain (1). A recent study showed excessive endothelial nitric oxide production and enhanced sensitivity of the endothelium in overt hyperthyroidism, and suggested that vascular endothelium may be a specific target for thyroid hormones (22). The persistent postural decrease in systolic BP despite restoration of biochemical euthyroidism reported here implies ongoing abnormalities of vascular endothelial function. Two recent studies have suggested abnormal endothelial function in overt hyperthyroidism, persisting even after effective treatment by antithyroid therapy (23,24); in contrast, Napoli et al. (22) found abnormal endothelial function in overt hyperthyroidism corrected after restoration of euthyroidism. Dehydration and deconditioning as a cause of the orthostatic changes in BP were considered unlikely because changes in vascular resistance are well described in hyperthyroidism, none of the subjects were clinically dehydrated, and all were ambulatory at investigation.

After sinus tachycardia, AF is the most common dysrhythmia in hyperthyroidism with incidence increasing with age (1,25,26). The prevalence of AF in our hyperthyroid cohort was 7.3%; previous studies have reported prevalences of 5% to 15%, but these have mostly been small (27) and retrospective in design (25,26). A recent large but retrospective study of hyperthyroid subjects found a prevalence of AF/atrial flutter of 8.3% (28), in keeping with the present study. Treatment of hyperthyroidism has been reported in one study to lead to spontaneous reversion to sinus rhythm in nearly two-thirds of patients within 8 to 10 weeks with virtually none reverting spontaneously beyond 3 months (29). In our study, most PAF resolved (evaluated on Holter monitoring) when patients became euthyroid, but newly diagnosed persistent AF resolved in only 5 of 15 cases; previously known AF resolved rarely (1 of 8 cases). An older study found the rate of spontaneous reversion was higher in the young and in men, whereas the presence of congestive cardiac failure adversely affected reversion to sinus rhythm (26). We found that those reverting to sinus rhythm were younger and that almost all had newly diagnosed AF. Known vascular disease, gender, and serum-free T_4 at presentation did not affect the likelihood of reversion. An initial hypothyroid state independently predicted successful reversion to sinus rhythm, a finding supported by a previous

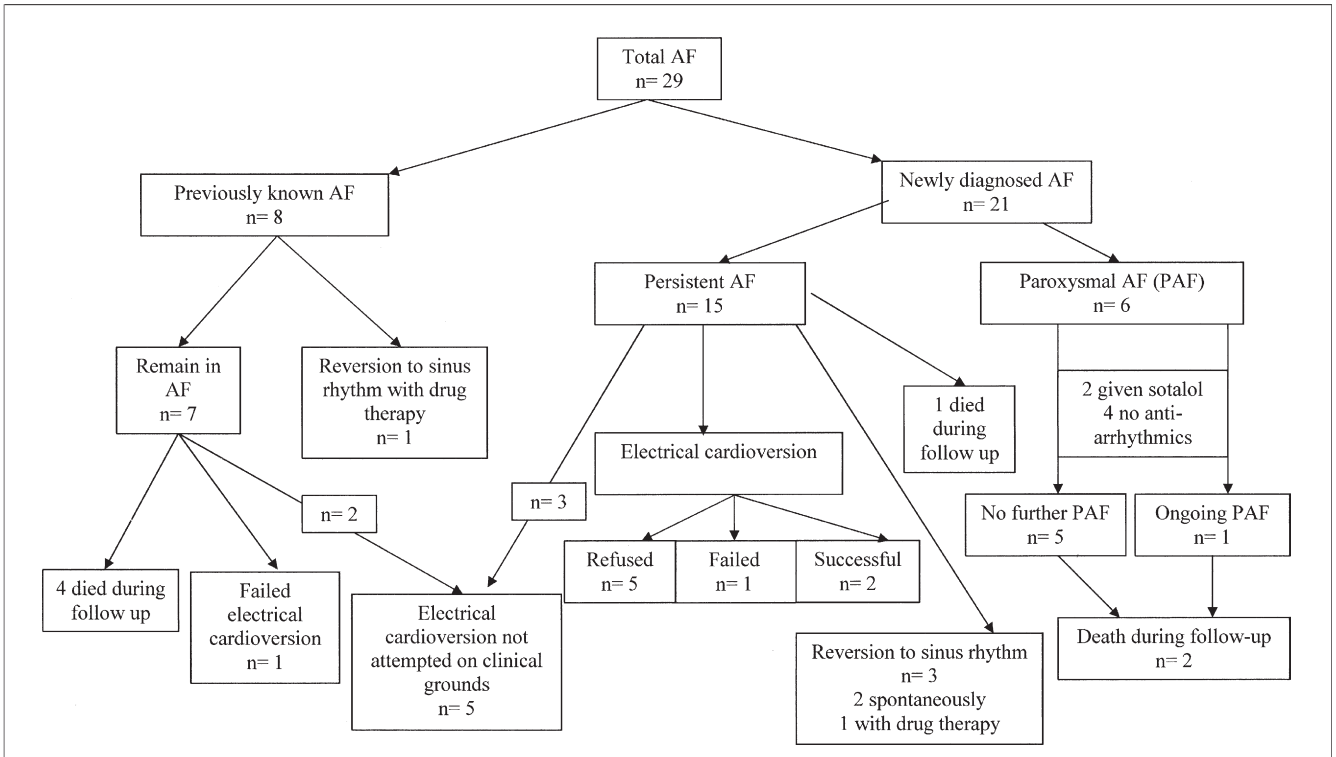

Figure 1 **Treatment and Outcome of Hyperthyroid Patients With AF**

AF = atrial fibrillation; PAF = paroxysmal atrial fibrillation.

study of 20 hyperthyroid subjects with AF rendered promptly hypothyroid (30); this hypothyroid state may be important in reducing tissue concentrations of thyroid hormones and facilitating a return to sinus rhythm, suggesting that those with AF and hyperthyroidism should be actively rendered hypothyroid in the short term, if tolerated, in an attempt to facilitate reversion to sinus rhythm.

The T_3-responsive genes encode both structural and regulatory proteins in the heart, such as myosin heavy chain, sarcoplasmic reticulum calcium adenosine triphosphatase, beta-adrenoceptors, sodium-potassium adenosine triphosphatase, and voltage gated potassium channels (1). Whether changes in these genes persist after antithyroid therapy and contribute to persisting AF remains to be evaluated. Thyroid hormone also affects extranuclear sites in the cardiac myocyte, influencing primarily the transport of amino acids, sugars, and calcium across the cell membrane (31,32). The T_3 can also alter the function of a number of ion channels in the cell membrane directly (including sodium, potassium, and calcium), and potentially can predispose to the development of AF (33). All of these effects of thyroid hormones are likely to have an influence on electrical remodeling of the myocardium.

Supraventricular dysrhythmias were prevalent in overt hyperthyroidism (regardless of its etiology) and persisted during antithyroid therapy; they are known to initiate AF in some patients (34). There are a few studies involving small numbers of subjects using Holter monitoring to determine the prevalence of dysrhythmias in hyperthyroid patients (15). Ventricular dysrhythmias were not more prevalent in hyperthyroidism in the present study, a finding consistent with previous small studies (15,35). The pathophysiology of supraventricular and ventricular arrhythmias differs in multiple respects, but the reason for the discrepancy observed in hyperthyroidism remains unclear. We evaluated treated hyperthyroid patients after a relatively short period after restoration of biochemical euthyroidism. Further longer-term follow-up of the cohort will help clarify whether cardiovascular manifestations noted after antithyroid therapy persist in the longer term and specifically whether this persistence might contribute to the long-term morbidity and mortality that we and others have shown in previous studies (3–5).

Subclinical hyperthyroidism is increasingly recognized as having significant consequences on the cardiovascular system, with increased morbidity (36,37) and mortality (38). Those with subclinical hyperthyroidism during follow-up in the present study had persisting cardiovascular symptoms and hemodynamic disturbances, even after those with vascular disease were excluded. These persisting abnormalities may reflect the preceding overt thyroid hormone excess and a delay in restoration of complete biochemical (or tissue) normality despite restoration of circulating thyroid hormone concentrations to normal. The present findings are in

keeping with those of previous studies evaluating both endogenous (39,40) and T_4-induced subclinical hyperthyroidism (41–43), although these studies generally examined subclinical hyperthyroidism of a greater duration than that observed during treatment of overt hyperthyroidism. Endogenous subclinical hyperthyroidism is known to be a risk factor for subsequent development of AF (36,37), but studies evaluating other dysrhythmias in these patients have been small and have had conflicting findings (39,40).

Study limitations. Some of the differences noted between the hyperthyroid and control cohorts may have been influenced by recruitment and ascertainment bias. However, we attempted to minimize these effects by recruiting an unselected consecutive hyperthyroid cohort representing all subjects with the diagnosis referred to a specialist clinic and by recruiting control subjects from a variety of sources. The similarity of covariates between the hyperthyroid and control cohorts suggests that the observed differences reflect the hyperthyroid state. Although the current study found persisting cardiovascular abnormalities, such as symptoms and AF, this was after a relatively short period of follow-up and these differences may not be sustained. Although a difference in mortality for the 2 groups was shown after a longer period of follow-up, the number of deaths remained too small to determine whether excess mortality was specifically vascular in nature.

Conclusions. Cardiovascular symptoms and signs, abnormal hemodynamics, and cardiac dysrhythmias are common in overt hyperthyroidism, and furthermore, these persist after antithyroid therapy has restored the circulating thyroid hormone concentration to normal. Risk factors predicting AF associated with hyperthyroidism were identified.

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